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(54) Title: N–ALKYLATION OF 5–AMINO–2,4,6–TRIIODO–ISOPHTHALAMIDES

(57) Abstract

The present invention provides a process for the preparation of a non–ionic 5–(N–2, 3–dihydroxypropyl –acylamino)–2,4, 6–triiodo–N,N'–disubstituted –isophthalamide which process comprises reacting a non–ionic 5–acylamino–2, 4,6–triiodo–N, N'–disubstituted –isophthalamide with an oxirane in a solvent and in the presence of up to 7 mole percent of a strong base.

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N-Alkylation of 5-Amino-2,4,6-triodo-isophthalamides

Field of the Invention

The invention relates to a process for the N-alkylation of a non-ionic 5-amino 2,4,6-triiodo-isophthalamide by base-catalysed reactions with an oxirane.

Background to the Invention

The use of non-ionic iodinated aromatic compounds as contrast agents in X-ray imaging (eg. CT-imaging) is well established. Several such contrast agents are available commercially, eg. iohexol, iopentol, ioxilan, iodixanol, iopamidol and ioversol.

The non-ionic iodinated contrast agents have to a large extent replaced the earlier generation ionic contrast agents, at least for parenteral use.

While the X-ray opacity of such agents derives from the presence of the iodine atom in the contrast agent molecule, the water-solubility of the non-ionic agents derives from the substitution of the aromatic ring with polyhydroxyalkyl groups. By way of example in the case of iohexol, the aromatic ring carries three 2,3-dihydroxypropyl groups (as substituents on amide nitrogens).

In the commercial manufacture of iohexol, and other non-ionic X-ray contrast agents, one of these 2,3-dihydroxy-propyl groups is introduced in one of the final steps in the multistep synthesis of the chemical drug product.

Conventionally, this 2,3-dihydroxypropyl group is introduced by reaction of a 5-acylamino-2,4,6-triiodo-isophthalamide with chloro-2,3-propanediol (CPD) in the presence of a base (eg. NaOH).

This procedure however results in the formation of equimolar quantities of salt which must be removed from the reaction product before it can be used as a non-ionic contrast agent or before it can be used in further process steps. Since the reaction product is highly water soluble, this removal of salt is not a trivial problem and requires the use of resin treatment and alcoholic work-up or of reverse osmosis. It should be noted that salt by-products are significantly more problematical with the non-ionic iodinated contrast agents than with the earlier ionic agents as the option to purify by crystallization is not so readily available. Moreover the solubility of the non-ionic iodinated contrast agents in water is similar to that of salt and so fractional crystalization is not a useful option.

In any commercial process for pharmaceutical preparation, there is a need to maximize product yield, avoid the production of impurities and optimize the use of reactors and work-up apparatus.

The present invention addresses the problem of salt generation in the N-2,3-dihydroxypropylation of 5-acylamino-2,4,6-triiodo-N,N'-disubstituted isophthalamides.

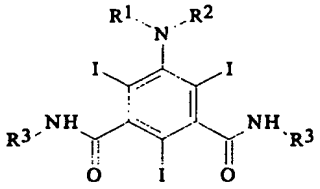
Summary of the Invention

Thus viewed from one aspect the invention provides a process for the preparation of a non-ionic 5-(N-2,3-dihydroxypropyl-acylamino)-2,4,6-triiodo-N,N'-disubstituted-isophthalamide which process comprises reacting a non-ionic 5-acylamino-2,4,6-triiodo-N,N'-disubstituted-isophthalamide with an oxirane (eg. glycidol) in a solvent and in the presence of up to 7 mole percent (relative to the 5-acylamino reagent), eg. 0.01 to 7 mole percent, of a strong base.

Surprisingly, the process of the invention makes it possible to quench in a controlled way the excess alkoxide anion which is formed in the reaction, leaving enough unquenched to remove acidic protons or nitrogens and providing the appropriate amount of acetyl-N anion to achieve selectivity. It is thus possible to achieve selectivity with a good reaction rate without provoking undesired side-reactions.

Detailed Description of the Invention

The 5-acylamino-isophthalamide starting reagent in the process of the invention is preferably a compound of formula I



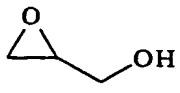
(I)

(where R^1 is an acyl group, preferably a formyl group or a (C_{1-6} alkyl)-carbonyl group in which the alkyl moiety is optionally hydroxy substituted, eg. a formyl, acetyl, propionyl, lactoyl, glycoloyl, or glyceroyl group;

R^2 is an oxirane-reactive (eg. glycidol-reactive) group or atom, preferably a hydrogen atom; and

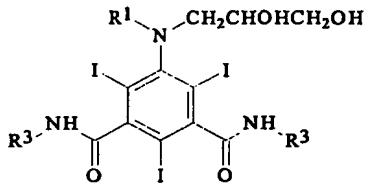
each R^3, which may be the same or different, is C_{1-6} acyl or alkyl group, preferably an acetyl or hydroxy-C_{1-6}-alkyl group, particularly preferably a polyhydroxyalkyl group, eg. 2,3-dihydroxypropyl, 1,3-dihydroxyprop-2-yl, 2-hydroxy-3-methoxypropyl, 2,3-dihydroxy-1-hydroxymethylpropyl and 2-hydroxyethyl).

The other reagent is glycidol of formula II



or an oxirane, eg. oxirane or a 2-acyl-oxirane.

Using a starting material of formula I and glycidol, the N-alkylated product is of formula III



(where R^1 and R^3 are as defined above).

The starting 5-acylamino-isophthalamide is particularly preferably 5-acetylamino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide.

The process of the invention is preferably performed in an aqueous or alkanolic solvent or solvent mixture (eg. water, methanol, 2-methoxyethanol, t-butanol, diglyme, etc.) or in a dipolar aprotic solvent or solvent mixture (eg. acetone, DMSO, DMF, DMAc etc.) or in a mixture of such solvents (eg. water/acetone, etc.). Tertiary alcohols in general (eg. t-butanol) are usable as solvents. The reaction product is typically highly soluble in such solvents and solvent mixtures, indeed it is generally more soluble than the 5-acylamino-isophthalamide reagent and thus the reaction can be performed with the reagents in solution or in a slurry. The quantity of solvent used may if desired be minimized, eg. being selected to be sufficient to maintain the reaction product in solution at the reaction temperature.

The 5-acylamino-isophthalamide and glycidol reagents are conveniently used in molar ratio of from 2:1 to 1:2, preferably 1:1 to 1:1.3, especially preferably about 1:1

to 1:1.1. These reagents are advantageously present in the reaction medium at a concentration of from 0.9 to 2M, especially 1.0 to 1.5M.

The base used to catalyse the process of the invention is a strong base, eg. NaOH, KOH, $Mg(OH)_2$, triethylamine, BuLi, sodium methoxide, sodium ethoxide, sodium propoxide, potassium tert.butoxide. Sodium and potassium hydroxides and alkoxides are particularly suitable. Particularly desirably it should be a base which is physiologically tolerable or which has physiologically tolerable neutralisation products or which is readily removed from the reaction product, eg. by solvent separation techniques, or by application of reduced pressure, eg. the base is quenched out in the water soluble phase after the reaction is completed. Especially preferably, the base is triethylamine.

Particularly preferably, the base is a material which does not separate out from the reaction mixture with the N-alkylated reaction product.

The base is used in catalytic quantities, eg. up to 7 mole %, preferably 0.01 to 7 mole %, more preferably 0.05 to 5 mole %, especially 0.5 to 4, more especially 1.0 to 3.5 mole % relative to the 5-acylamino-isophthalamide starting reagent.

The reaction between the glycidol and 5-acylamino-isophthalamide is conveniently effected at ambient or slightly elevated temperatures, eg. 10 to 50°C, preferably 15 to 30°C, especially preferably 20 to 25°C.

The reaction is allowed to proceed until analysis of samples of the reaction mixture shows the concentrations of reagents and reaction product to have stabilized. Typically, the reaction time may be a period of hours, eg. 6 to 20 hours.

The reaction may be terminated by warming the reaction mixture eg. to 50 to 70°C, especially about 60°C and diluting it with a solvent in which the reaction product is less soluble whereby to cause the reaction product to separate out.

By adding a solvent which reduces the solubility of the N-2,3-dihydroxypropylated reaction product in the solvent system, the reaction product (and the 5-acylamino-isophthalamide reagent) can be caused to separate out from the solvent system while leaving the base catalyst and any excess unreacted glycidol in solution; in this way a substantially base-free reaction product can be obtained without requiring particularly extensive work-up.

The reaction product can then be worked-up and purified in conventional fashion, for example by recrystallization of unreacted 5-acylamino reagent from a solvent such as water or an alkanol, followed by solvent evaporation to yield the reaction product.

In this way the use of expensive deionizing techniques, such as reverse osmosis or the use of ion exchange resins, required by the conventional N-2,3-dihydroxypropylation processes is avoided.

The invention will now be described further with reference to the following non-limiting Example.

Example 1

5-(N-2,3-dihydroxypropyl-acetamino)-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide

74.7 grams of 5-acetamino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide, 75 mL dimethyl-sulphoxide, and 7 mL triethylamine was stirred and warmed to 70-80°C before being cooled to ambient temperature. A single addition of 7 mL of glycidol was made and the reaction mixture was stirred overnight.

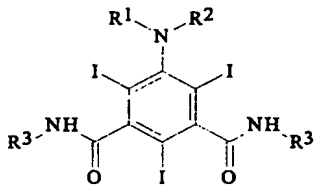
The reaction mixture was then warmed to 60°C and diluted with 400 mL of isopropanol. An oily product separated out and solidified upon cooling. The liquor was decanted and the solid product was dissolved in warm water, seeded with 5-acetamino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide and chilled in an ice bath. A solid crystallized and was separated off by filtration. (This solid was 22.5 gram of unreacted 5-acetamino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide.

The filtrate was evaporated down to leave the title compound as a residual oil weighing 56.7 grams.

Claims

1. A process for the preparation of a non-ionic 5-(N-2,3-dihydroxypropyl-acylamino)-2,4,6-triiodo-N,N'-disubstituted-isophthalamide which process comprises reacting a non-ionic 5-acylamino-2,4,6-triiodo-N,N'-disubstituted-isophthalamide with an oxirane, preferably glycidol, in a solvent and in the presence of up to 7 mole percent, relative to the 5-acylamino isophthalamide, of a strong base.

2. A process as claimed in claim 1 wherein said 5-acylamino-isophthalamide is a compound of formula I



(I)

(where R^1 is an acyl group, preferably a formyl group or a (C_{1-6} alkyl)-carbonyl group in which the alkyl moiety is optionally hydroxy substituted;

R^2 is a glycidol-reactive group or atom, preferably a hydrogen atom; and

each R^3, which may be the same or different, is an optionally hydoxylated C_{1-6} acyl or alkyl group).

3. A process as claimed in claim 1 for the preparation of 5-(N-2,3-dihydroxypropyl-acetamino)-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide wherein said 5-acylamino-isophthalamide is 5-acetamino-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)-isophthalamide.

4. A process as claimed in any one of claims 1 to 3 wherein as said base is used 0.01 to 7 mole % of a strong base.

5. A process as claimed in claim 4 wherein said base comprises triethylamine.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/GB 98/03535

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C231/12 C07C233/05 C07C233/65 A61K31/165 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and. where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document. with indication. where appropriate. of the relevant passages	Relevant to claim No.
X	WO 96 40286 A (MALLINCKRODT MEDICAL INC) 19 December 1996 see claims 1,6,9; example 7; table II	1-5
X	WO 97 27172 A (MALLINCKRODT MEDICAL INC :DUNN THOMAS JEFFREY (US); WHITE DAVID H) 31 July 1997 see page 8 - page 9; claims 1,6; example 5	1-5
X	DE 27 26 196 A (NYEGAARD & CO AS) 22 December 1977 see page 18; claims 5,6	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

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